REMARKS/ARGUMENTS

In response to the Office Action of August 8, 2006, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on September 22, 2003).

Claims 1 and 39-46 remain pending in the instant application and are currently under examination.

No new matter has been added by the amendment to the specification made herein.

The paragraph beginning at page 24 has been amended to correct a typographical error (luymph to lymph).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to recite that the biopolymer marker consisting of SEQ ID NO:1 is indicative of insulin resistance. The instant specification discloses that this biopolymer marker was found to be related to insulin resistance(Figure 1 and page 46, lines 4-11).

Claim 39 has been amended to clarify that the claimed method

involves comparing the characteristic mass spectral profile of the biopolymer marker consisting of SEQ ID NO:1 (shown in Figure 2) to profiles obtained from a mass spectrometric analysis of an unknown sample in order to determine if the claimed biopolymer marker is present in the sample and thus indicative of insulin resistance in the patient from whom the sample was obtained. This determination is made by matching the reference mass spectral profile (shown in Figure 2) to a mass spectral profile obtained from the unknown sample. Claim 39 has also been amended to recite the steps (chromatography, electrophoresis, enzymatic digestion) used to prepare a sample for analysis by mass spectrometry. These preparatory steps increase the range, i.e. maximize elucidation, of peptides present in different concentrations that can be identified from a sample. See the abstract; page 24, line 14 to page 25, line 18; page 35, lines 19-22 and page 40, line 8 to page 46, line 3 of the instant specification as originally filed.

Claim 44 has been amended to correspond with the method of claim 39 as amended herein; i.e. claim 44 as amended herein is drawn to kit which is useful for carrying out the method of claim 39.

* Please note that the Examiner's comments, as reiterated herein, are single spaced to clearly delineate the Examiner's comments from Applicants' comments.

Rejection under 35 USC 101

Claims 1 and 39-46, as presented on July 12, 2005, stand rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a substantial, credible or a well-established utility.

Claim 1 is drawn to a biopolymer marker consisting of SEQ ID NO:1 and a method of using. The instant claims and the specification assert that the biopolymer marker is recited to be useful in methods determining the differential expression/absence/presence of SEQ ID NO:1 that asserts a linkage or association with insulin resistance.

The Examiner states that Applicant has disclosed in the specification that SEQ ID NO:1 is differentially measurable in patients with insulin resistance in comparison to sample from normal patients (page 46, lines 4-11). Applicant's have disclosed in the remarks/arguments (page 24, paragraphs 1-3) that the marker is present in one patient with insulin resistance and absent in the other patient with insulin resistance. Applicant's have also disclosed that the marker is absent in the patients with Diabetes I and Diabetes II (see Figure 1 and applicant's arguments page 22). Therefore, the Examiner asserts that the differential expression of SEQ ID NO:1 is not evident and the data results are ambiguous. The Examiner maintains that the correlation with respect to insulin resistance is not exemplified or disclosed in the specification. With respect to page 46 of the specification that discloses markers can be differentially expressed in disease states is noted, however the SEQ ID NO:1 that applicant recites has not been shown to be linked to insulin resistance because the marker is expressed in all normal sample and one sample of insulin resistance and not in the other patient with insulin resistance. Therefore, the Examiner concludes that the teaching is ambiguous and one of ordinary skill in the art would not be able to distinguish a credible, substantial and specific utility that SEQ ID NO:1 is linked to insulin resistance. One of ordinary skill in the art could not distingusih if the marker is linked to insulin resistance, diabetes I or diabetes II. Although the MPEP does not require examples, however, the teaching provided must be substantial enough to enable one of ordinary skill in the art to ascertain the credibility of the evidence presented. Accordingly, the Examiner concludes that the specification does not identify a substantial, credible or well-established utility for a sequence consisting of SEQ ID NO:1 and methods of use including the claimed kit consisting of SEQ ID NO:1.

In the section of the Office Action entitled "Response to

Arguments" number 6, the Examiner asserts that Applicant's argument that the claims have been amended to remove the term "diagnostic" and have established that the biopolymer marker consisting of SEQ ID NO:1 is indicated as linked to insulin resistance have been considered, but not found to be persuasive for reasons set forth in the newly applied utility rejection.

In the section of the Office Action entitled "Response to Arguments" number 7, the Examiner states that Applicant argues that claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:1 and does not recite that the claimed peptide is diagnostic for insulin resistance nor does it recite that SEQ ID NO:1 is related to insulin resistance. Applicant further contends that the specification fully supports that SEQ ID NO:1 is diagnostic of and linked to insulin resistance. Applicant asserts that the closed language "consisting of" limits the scope of SEQ ID NO:1 only to the specific peptide. This argument is noted but not found to be persuasive.

In response, the Examiner asserts, that although claim 1, does not recite that SEQ ID NO:1 is linked to insulin resistance, nor does claims 44-46 which are drawn to a kit consisting of SEQ ID NO:1, claims 39-43 are drawn to a method of determining SEQ ID NO:1 reciting a link to insulin resistance; the specification also asserts that insulin resistance is the claimed utility for SEQ ID NO:1. Thus, the Examiner has applied a utility rejection.

In the section of the Office Action entitled "Response to Arguments" number 8, the Examiner asserts that Applicant argues that peptides that are differentially expressed between a disease state and a normal physiological state are often determined to be associated with the disease state. Applicant further argues that the claimed biopolymer marker peptide is identified in all of the normal samples and in one disease sample and likewise is absent in four disease samples; thus, the instant inventors link the claimed biopolymer marker peptide with insulin resistance. The argument is noted but is not found to be persuasive.

In response, the Examiner maintains that one of ordinary skill in the art could not ascertain a substantial, well-established or credible utility for SEQ ID NO:1 being linked to insulin resistance, diabetes I or II, because the marker is expressed in all of the normal samples and one sample of insulin resistance and not in the others (see Figure 1). The Examiner asserts that the teaching of the specification is ambiguous because it does not clearly show that SEQ ID NO:1 is linked to insulin resistance. The Examiner maintains that one of ordinary skill in the art would not be able to distinguish a credible, substantial and specific utility linked to insulin resistance. The Examiner does not dispute the protocols used in identifying differentially expressed markers to

identify a link to a disease state, however, the utility must be specific, credible and well-established.

Applicants respectfully disagree with all of the Examiner's assertions.

Rejections under 35 USC 101 have rarely been sustained by the courts because an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement; i.e the Office should presume that a statement of utility made by an applicant is true (see MPEP 2107.02 III A and *In re Langer* 183 USPQ 297).

Thus, the Examiner should properly presume that the differential expression of the claimed biopolymer marker (SEQ ID NO:1) as exemplified in Figure 1 links the marker to insulin resistance.

It is well known that pathological changes in an organism are reflected by changes observed in the serum protein pattern. In other words, proteins that undergo a change in expression (from the normal) are often indicative of disease. A diagnosis may be predicted based upon the similarity of an unknown sample pattern to a known pattern of disease. Mass spectrometry is a tool used to establish serum protein patterns.

Generally proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are

often first subjected to separation by polyacrylamide gel electrophoresis. The separated protein bands which are deemed to be different between two comparable states are excised from the gel and subjected to further fragmentation by enzymes. These resulting peptides are then collected and purified by chromatography prior to identification by mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The mass spectral profiles generated are composed of parts of the original protein. See page 37, line 23 to page 40, line 6 of the instant specification.

In order for a rejection under 35 USC 101 to be appropriate, the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention (see *In re Joyce A. Cortright* 49 USPQ 2d 1464 1999).

It is respectfully submitted that the "link to insulin resistance" asserted by Applicants was elucidated under real-world conditions according to the methodology set forth in the following steps:

I) isolating peptides from body fluid samples obtained from four groups of patients,

i) one group known to suffer from insulin resistance;

ii) one group known to suffer from Type I diabetes;

iii) one group known to suffer from Type II diabetes; and

iv) one group of "normal" patients (healthy controls);

II) carrying out the protocols disclosed in the specification (see pages 37-47);

III) comparing the expression of protein bands from the four groups of patients as evidenced in gels (such as that shown in Figure 1);

IV) subjecting the observed expression pattern to the criteria as disclosed at page 11, lines 9-20 of the instant specification;

V) excising bands that are differentially expressed between the groups, and, submitting the peptides present within the excised bands for sequence identification by mass spectrometry.

The instant inventors, using the above-described methodology in a real-world environment, thereby elucidated and identified SEQ ID NO:1 as a fragment of apolipoprotein A-IV precursor protein showing differential expression between a normal state and a diseased state. Thus, the instantly claimed link to insulin resistance was established as evidenced by the observed differential expression. Applicants respectfully submit that the "link to insulin resistance" ,evidenced by the differential expression shown in Figure 1, supports the usefulness of the claimed peptide (SEQ ID NO:1) for diagnosis and/or treatment of

insulin resistance.

In order to further illustrate the differential expression, Applicants provide the attached Declaration (and figure) under 37 CFR 1.132. The figure attached to the declaration is entitled "HiQ 1-(Elution) Insulin Resistance vs. Normal" and represents Figure 1 as originally filed in the instant application. The figure attached to the declaration was produced by scanning the original photograph of the gel. Expression of Band 7, from which the claimed peptide (SEQ ID NO:1) was identified, is shown in all of the samples obtained from normal patients (lanes 7-9) and in one of the samples obtained from patients having insulin resistance (lane 3). In contrast, expression of Band 7 was not found in any of the samples obtained from patients having diabetes (lanes 2, 5 and 6) or in one of the samples obtained from patients having insulin resistance (lane 4). Thus, contrary to the Examiner's assertion, the differential expression of the claimed biopolymer marker (SEQ ID NO:1) is evident.

No new matter has been added with the declaration; the figure attached thereto is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (SEQ ID NO:1). The gel shown in the figure does not represent new experimentation; the figure shows only a clearer image of the original gel made at the

time that the experiments described in the instant specification were first carried out.

Figure 2 shows a mass spectral profile of a peptide obtained from Band 7 of the gel shown in Figure 1. This mass spectral profile is the characteristic mass spectral profile for the claimed biopolymer marker, a fragment of apolipoprotein A-IV precursor having a molecular weight of about 1312 daltons and identified as SEQ ID NO:1. Mass spectral profiles are reproducible, and are typically published for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profiles provided in the instant specification as references for comparing with mass spectral profiles of peptides obtained from unknown samples to test the unknown samples for a link to insulin resistance, thereby establishing a disclosed specific and substantial credible utility.

Accordingly, Applicants respectfully submit that the Examiner has failed to demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.

The Examiner asserts that the data results are ambiguous because the marker is expressed in all normal samples and in one insulin resistance sample and not in the other patient with insulin resistance.

If an Examiner doubts the credibility of an asserted utility,

the Examiner must show that the asserted utility is wholly inconsistent with contemporary knowledge in the art (see *In re Gazave* 379 F.2d 973, 978 CCPA 1967).

Applicants do not intend for the term "biopolymer marker" to be limited to expression in a disease state and absence in normal, any differential expression can link a peptide to a disease state (see page 5, lines 12-20 and page 11, lines 9-20 of the instant specification); for example, the claimed peptide (SEQ ID NO:1) is termed a "biopolymer marker" because while it is found in both disease and normal, expression is decreased in disease.

Applicants respectfully submit that such a description of biopolymer markers is acceptable in the art. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103(4):433-446 1996; reference 1) identify homovanillic acid as a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in age-matched control patients.

Recognizing that insulin resistance is characteristic of the early stages of Syndrome X and furthermore recognizing that insulin resistance often leads to the development of overt diabetes, the inventors were interested in the identification of protein markers for insulin resistance; see the specification at page 30, line 8

to page 31, line 3. Insulin resistance is defined as impaired insulin-stimulated glucose utilization; one suffering from insulin resistance will require an increased quantity of insulin to maintain metabolic control of glucose. Subsequent increases in insulin secretion result in hyperinsulinemia, which is considered to be a significant risk factor for the development of NIDDM (non-insulin dependent diabetes mellitus or Type II diabetes). See the attached article of Falkner et al. accessed from the internet and published in *Arteriosclerosis, Thrombosis, and Vascular Biology* 15:1798-1804 1995; reference 2.

Currently, diseases are most easily diagnosed in their later stages, but controlling them at a late stage is extremely difficult. Disease prevention is much more effective at an earlier stage (see the instant specification at page 31, lines 5-8). Considering that insulin resistance is a known risk factor for the development of Type II diabetes; the condition is expected to be present in the early stages of the disease (Type II diabetes). Thus, the identification of markers for insulin resistance can lead to prevention of and/or more effective treatment for Type II diabetes. Accordingly, Applicants were motivated to pursue such markers.

Considering that insulin resistance is known to lead to Type II diabetes, a marker for insulin resistance, that is absent and/or

exhibits decreased expression in disease, could be expected to be present in normal samples, absent in diabetes and variably present in insulin resistance depending on the stage of disease progression. Thus, the differential expression pattern observed by the instant inventors is what could be expected based upon what is known in the art regarding the relationship of insulin resistance to diabetes.

Accordingly, Applicants respectfully submit that the Examiner has failed to show that Applicants' asserted utility for the claimed marker (SEQ ID NO:1) is wholly inconsistent with contemporary knowledge in the art.

An Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe applicant's assertion of utility (see *In re Brana* 34 USPQ 2d 1436).

Although the prior art does not specifically recognize that the claimed biopolymer consisting of SEQ ID NO:1, a fragment of the apolipoprotein A-IV precursor protein, is related to insulin resistance, it does recognize the link between insulin resistance, an altered plasma lipid profile and Type II diabetes (see attached abstract of Serrano Rios (European Journal of Clinical Investigation 28:14 1998; reference 3). Furthermore, it is known that apolipoprotein A-IV genetic polymorphisms are associated with

myocardial infarction in obese non-insulin dependent (Type II) diabetes patients (see attached abstract of Rewers et al. Diabetes 43(12):1485-1489 1994; reference 4). Thus, it is likely that the levels and/or function of apolipoprotein A-IV is altered in insulin resistance.

Applicants respectfully submit that an artisan of ordinary skill would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and insulin resistance to be reasonable. As was discussed extensively in the prior Response filed on July 12, 2005 (pages 24-28), when one of skill in the art observes the differential expression of the claimed biopolymer marker (SEQ ID NO:1) between insulin resistance, diabetes and normal patients; one of skill in the art will connect this marker with diagnostics and/or therapeutics for insulin resistance.

At page 46 of the specification as originally filed , SEQ ID NO:1 is identified as a fragment of apolipoprotein precursor protein. As mentioned above, insulin resistance, an altered plasma lipid profile and Type II diabetes are known to be linked (see reference 3). Additionally, genetic polymorphisms in the apolipoprotein A-IV gene could cause alterations in the function of the apolipoprotein A-IV protein, that in turn, could influence a disease state (see reference 4). One of ordinary skill in the art, considering the known involvement of apolipoprotein A-IV and

insulin resistance, upon observation of the differential expression of SEQ ID NO:1 in insulin resistance versus normal control, would find it reasonable to believe that this peptide is linked to insulin resistance.

Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not doubt the veracity of Applicants asserted utility for the claimed peptide (SEQ ID NO:1).

Furthermore, situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus expression in a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology

56(6):673-680 1999; reference 5).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be familiar with such practice (suggestion of a differentially expressed peptide for diagnostics) and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (SEQ ID NO:1) to the suggested use of diagnostics and/or therapeutics of insulin resistance is plausible.

It has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (see MPEP 2164.07 I C).

Figure 1 establishes that the claimed biopolymer marker (SEQ ID NO:1) is differentially expressed between insulin resistance patients, diabetes patients and normal patients. As pointed out above, one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Thus, differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease condition, no additional validation, comparison with other diseases, or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill in the art would believe, based upon the information in the specification in light of the knowledge in the prior art, that the claimed biopolymer marker (SEQ ID NO:1) is more likely than not to be a marker of insulin resistance.

The Examiner is reminded that the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research. The progress of science usually occurs in a "piecemeal" fashion; meaning that a "discovery" does not arise by itself but often proceeds through multiple "discoveries". For example, a new drug to treat insulin resistance is a "discovery" while peptide markers, such as the instant invention are smaller "discoveries". These smaller "discoveries" , such as the instant invention, should be allowed patent protection because they promote the progress of science by leading to further, larger "discoveries".

The decision in *In re Brana* (34 USPQ2d 1436 and MPEP 2107.01 III) lends support to this argument as well since the Federal Circuit stated that usefulness in patent law, and in particular in

the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer and/or in the instant case, isnulin resistance and diabetes.

Additionally, in contrast to the disputed matter in Fisher (see *In re Fisher* 76 USPQ 2d 1225 2005), where expressed sequence tags (ESTs) were deemed not to have a substantial and credible utility because the disclosed uses were not specific to the claimed ESTs but instead were generally applicable to any EST, the instantly claimed peptide exhibits a specific use as a marker linked to insulin resistance supported by data specifically directed to patients having insulin resistance.

As noted above, one could, without any further research, utilize the mass spectral profiles provided in the instant specification as references for comparing with mass spectral profiles of peptides obtained from unknown samples to test the unknown samples for a link to insulin resistance. Thus, the instant

invention satisfies the Fisher test for disclosure of a substantial utility by showing that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research, and thus, a significant and presently available "real-world" benefit to the public is disclosed.

In conclusion, based upon all of the above arguments, Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has a specific, substantial and well-established, credible utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejections under 35 USC 112, first paragraph

Claims 1 and 39-46, as presented on July 12, 2005, stand rejected under 35 USC 112, first paragraph. Specifically, since the claimed invention allegedly is not supported by either a substantial, credible or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has a clear substantial,

credible and a well-established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (SEQ ID NO:1) as a marker for insulin resistance and would further recognize how to use the mass spectral profile of the marker as disclosed in the specification for testing unknown samples for the presence of the biopolymer marker; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Claims 1 and 39-46, as presented on July 12, 2005, stand further rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as the enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Although one of ordinary skill in the art can make or reproduce SEQ ID NO:1, the specification does not have sufficient teaching on how to use the biopolymer marker consisting of SEQ ID NO:1/ Factors that the Examiner considers in determining whether a disclosure requires undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3)the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The Examiner asserts that claims 1 and 39-46 are directed to a biopolymer marker consisting of SEQ ID NO:1 associated with insulin resistance. However, the specification does not support this assertion. The specification (in particular page 46) and the figures do not definitively correlate differential expression of the claimed marker consisting of SEQ ID NO:1 in insulin resistance in comparison to samples from normal patients and patients with diabetes I and II.

There is no sufficient teaching in the specification that

would enable one to choose SEQ ID NO:1 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample. There is no correlation between the procedure for screening samples from patients suspected of having insulin resistance or diabetes I or II.

Furthermore, the Examiner asserts that Applicants have not provided any disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence. The disclosure is equally lacking any teaching for how the identified sequence will be utilized to identify a link to insulin resistance.

Applicants have not set forth any supporting evidence that suggests that SEQ ID NO:1 is associated with insulin resistance or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

Tockman et al. (Cancer Research 52:2711s-2718s 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other disorders.

Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (page 2714s, column 1).

The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section.

Tockman reiterates that the predictability of the art in

regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

The instant disclosure has not addressed the issues taught in the prior art as crucial to the discovery of the biopolymer marker.

The predictability or lack thereof in the art -there is no predictability based on the instant specification that the biopolymers are indicative of any disease state including insulin resistance.

The quantity of experimentation necessary -it would require undue amount of experimentation for the skilled artisan to use the biopolymers as claimed.

While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breath of the claimed biopolymer is enabled for its use. The Examiner asserts that this is not the case in the instant specification.

The Examiner concludes that, in view of the teachings of *In re Wands*, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breath of the claims is undue.

In the section of the Office Action entitled "Response to Arguments" number 9, the Examiner asserts that Applicant argues that the declaration under 37 CFR 1.132 filed on September 22, 2003 is insufficient to overcome the rejection of claims 1 and 39-46 based on the 112 first rejection as set forth in the last Office Action, dated December 3, 2003, because Figure 1 is not ambiguous. This argument is noted but not found to be persuasive.

In response, the Examiner states that although a total enablement rejection was applied in the previous Office Action, the previous enablement rejection is hereby withdrawn on the basis of a protocol of making a peptide. However, the basic thrust of the rejection is the same. The Examiner has modified the rejection on the basis of not having a specific, well-established or substantial utility (see above utility rejection) and since utility is use, which is part of a 112 first paragraph enablement rejection, applicant is not enabled for its use.

In the section of the Office Action entitled "Response to Arguments" number 10, the Examiner asserts that Applicant argues that the Tockman et al reference was not relevant to the instant invention because they do not teach SEQ ID NO:1 linked to insulin resistance. The Examiner asserts that this argument has been considered but not found to be persuasive.

In response, the Examiner asserts that the references were cited to show the state of the art with respect to marker

discovery. A rejection is proper though a reference is not prior art when it establishes the level of ordinary skill in the art at the time of the claimed invention, *Ex parte Erlich,* 22 USPQ 2d 1463, 1465 (Board of Patent Appeals 1992). The Examiner asserts that the enablement issue is whether one skilled in the art could have used SEQ ID NO:1 as a link to insulin resistance without undue experimentation at the time that the application was filed. The Examiner asserts that the specification has not clearly set forth a link between the claimed sequence and insulin resistance, therefore undue experimentation is required and the rejection is hereby maintained.

Applicants respectfully disagree with all of the Examiner's assertions.

The Examiner states that although a total enablement rejection was applied in the previous Office Action, the previous enablement rejection is hereby withdrawn on the basis of a protocol of making a peptide. However, the basic thrust of the rejection is the same. The Examiner has modified the rejection on the basis of not having a specific, well-established or substantial utility (see above utility rejection) and since utility is use, which is part of a 112 first paragraph enablement rejection, applicant is not enabled for its use.

First, Applicants assert that it has been established by prior arguments in the instant response that the claimed invention has a clear substantial, credible and a well-established utility. The data presented in the instant specification, which shows the differential expression of the claimed peptide, supports Applicants' assertion of the association of the claimed peptide with insulin resistance. Furthermore, Applicants submit that the specification clearly discloses how to use the mass spectral profile of the claimed marker, shown in Figure 2, for testing unknown samples for the presence of the biopolymer marker, thus

linking the samples to insulin resistance.

The Examiner refers to a previously filed declaration and asserts that Applicant argues that the declaration under 37 CFR 1.132 filed on September 22, 2003 is sufficient to overcome the rejection of claims 1 and 39-46 based on the 112 first rejection as set forth in the last Office Action, dated December 3, 2003, because Figure 1 is not ambiguous. This argument is noted but not found to be persuasive.

This declaration clarifies the use of controls in the experiments described in the instant specification and was filed in response to the Examiner's allegation in the previous Office Action mailed on July 15, 2003, that these experiments lacked controls.

The Examiner asserts that Applicant argues that the Tockman et al reference was not relevant to the instant invention because they do not teach SEQ ID NO:1 linked to insulin resistance. The Examiner asserts that this argument has been considered but not found to be persuasive.

The Examiner asserts that the references were cited to show the state of the art with respect to marker discovery. A rejection is proper though a reference is not prior art when it establishes the level of ordinary skill in the art at the time of the claimed invention, *Ex parte Erlich,* 22 USPQ 2d 1463, 1465 (Board of Patent Appeals 1992).

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Examiner asserts that Tockman et al. show the state of the art with respect to marker discovery.

Applicants note that Tockman et al. was published approximately nine years before the time of the instant invention. Theories and standards change quickly in biotechnology, especially

over a decade.

Scott D. Patterson (article cited on page 24 of the previous Response filed on July 12, 2005) presents the state of art in mass spectrometry/proteomics in 2000, coinciding with the time that the instant inventors were working to develop their invention. Patterson establishes that the linking of biomarkers to disease through differential expression was commonly practiced in 2000.

Thus, Applicants respectfully submit that the article by Tockman et al. does not provide an accurate, up-to-date assessment of the "state of the art" at the time of the instant invention.

However, although a direct parallel can not be drawn between the neoplastic disease process (Tockman et al.) and the disease process of insulin resistance, a parallel can be drawn between the reasoning process of Tockman et al. and the reasoning process presented in the instant specification.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect

oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and insulin resistance.

In conclusion, based upon all of the above arguments and those

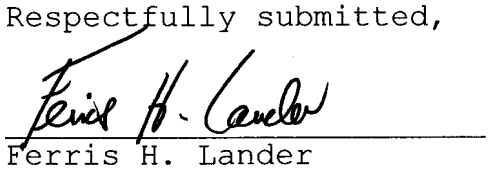
presented in prior Responses, Applicants assert that one could, without any further research, utilize the mass spectral profiles provided in the instant specification as references for comparing with mass spectral profiles of peptides obtained from unknown samples to test the unknown samples for a link to insulin resistance. Thus, the instant specification has clearly set forth a link between the claimed peptide (SEQ ID NO:1) and insulin resistance that enables the use of the peptide.

Accordingly, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendment to the specification, amendments to the claims and Declaration under 37 CFR 1.132, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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1: J Neural Transm. 1996;103(4):433-46.

Elevated 5-S-cysteinyldopamine/homovanillic acid ratio and reduced homovanillic acid in cerebrospinal fluid: possible markers for and potential insights into the pathoetiology of Parkinson's disease.

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Department of Medical Research and Geriatrics Medical Center, Taichung, Taiwan, Republic of China.

High-performance liquid chromatography with electrochemical detection has been employed to analyze ultrafiltrates of cerebrospinal fluid of Parkinson's Disease (PD) patients and age-matched controls for the dopamine (DA) metabolites homovanillic acid (HVA) and 5-S-cysteinyldopamine (5-S-CyS-DA). The mean level of HVA in the CSF of PD patients, measured 5 days after withdrawal from L-DOPA therapy, was significantly lower than that measured in controls. By contrast, mean levels of 5-S-CyS-DA were not significantly different in the CSF of PD patients taking L-DOPA (PD-LT patients) the same patients 5 days after discontinuing this drug (PD-LW patients) or controls. However, the mean 5-S-CyS-DA/HVA concentration ratio was significantly ($p < 0.05$) higher in the CSF of PD-LW patients compared to controls. Although the PD patient population employed in this study had been diagnosed with the disease several years previously and had been treated with L-DOPA for prolonged periods of time the results of this study suggest that low CSF levels of HVA and a high 5-S-CyS-DA/HVA ratio together might represent useful markers for early diagnosis of PD. The high 5-S-CyS-DA/HVA ratio observed in the CSF of PD-LW patients also provides support for the hypothesis that the translocation of glutathione or L-cysteine into neuromelanin-pigmented dopaminergic cell bodies in the substantia nigra might represent an early event in the pathogenesis of PD.

PMID: 9617787 [PubMed - indexed for MEDLINE]

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(*Arteriosclerosis, Thrombosis, and Vascular Biology.* 1995;15:1798-1804.)
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Articles

Insulin Sensitivity, Lipids, and Blood Pressure in Young American Blacks

Bonita Falkner; Harvey Kushner; Thomas Tulenko; Anne E. Sumner; Julian B. Marsh

From the Medical College of Pennsylvania, Philadelphia, and Hahnemann University, Philadelphia, Pa.

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Abstract

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Abstract The purpose of this study was to determine whether insulin resistance was linked with alterations in plasma lipids in adult young blacks with borderline hypertension. Ninety-four American blacks participated (46 men, 48 women, age range 28 to 33 years). Within this group of 94 subjects, there were 60 normotensive (Nt) subjects and 36 subjects with borderline hypertension (BHt), defined as blood pressure >135/85 mm Hg. None of the subjects were diabetic or receiving antihypertension medication. All participants had blood pressure and anthropometric measurements, a fasting lipid profile, an oral glucose tolerance test, and a euglycemic hyperinsulinemic clamp. Insulin-stimulated glucose utilization (M), determined by insulin clamp, was significantly lower in the BHt subjects compared with the Nt subjects (men, Nt 6.91±0.62 versus BHt 5.54±0.65; women, Nt 5.97±0.47 versus BHt 3.79±0.38 mg · kg^{-1} · min^{-1}, P=.006). When M was corrected for adiposity and expressed in milligrams per kilogram of fat free mass

(M'), the difference between Nt and BHt remained significant (P=.006). There was a significant correlation of M' with systolic blood pressure (r=-.393, P<.0001), HDL-C (r=.382, P<.0001), triglyceride level (r=-.308, P<.001), apolipoprotein A-I (r=.190, P=.033), and apolipoprotein B (r=-.277, P=.004). When all lipid variables were entered in a stepwise multiple linear regression analysis, HDL-C emerged as the most significant lipid component in the model for insulin resistance. These data suggest that in American blacks with mild hypertension, the risk for cardiovascular disease may be augmented in the presence of insulin resistance.

Key Words: blood pressure • insulin • lipids • blacks • African Americans

Introduction

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In the United States, the age-adjusted mortality rate for heart diseases is about 40% higher for American blacks than for whites.[1] The prevalence of the related disorders, essential hypertension, NIDDM, and obesity, which increase the incidence and accelerate the morbidity of heart disease, is also greater in blacks than in whites.[2] Longitudinal studies on cardiovascular disease in whites and blacks from Evans County, Georgia, have demonstrated that cardiovascular mortality was related to the presence of cardiovascular risk factors in both whites and blacks.[3 4]

Elevated plasma insulin concentration (hyperinsulinemia) and impaired insulin-stimulated glucose utilization, or insulin resistance, are strongly linked with cardiovascular diseases, including essential hypertension, NIDDM, and atherosclerosis.[5] Insulin resistance is a clinical phenomenon arising from a defect in the cellular response to insulin stimulation. Due to a peripheral cell defect in insulin-mediated glucose utilization, a greater quantity of insulin is necessary to achieve metabolic control of glucose, resulting in hyperinsulinemia.[5] Hyperinsulinemia, a characteristic feature of obesity and NIDDM, is also observed in hypertension independent of obesity and NIDDM.[6 7 8]

Several clinical investigations in young adult whites have demonstrated a direct correlation of plasma insulin concentration with BP suggesting that insulin could be a mediator of BP.[9 10] However, in a study by Saad et al[11] of obese normotensive whites, blacks, and Pima Indians, a significant correlation of insulin resistance with BP was present in the whites but not in the blacks or Pima Indians. In contrast, we have previously demonstrated a significant correlation of insulin resistance with BP in young adult blacks that was independent of obesity.[12 13]

In white and Hispanic populations, higher plasma insulin concentration is associated with an atherogenic lipid pattern including elevated LDL-C and VLDL-TG and decreased HDL-C.[14 15] The relation of plasma lipids with BP in the context of insulin resistance has not been examined in young blacks. The purpose of this study was to determine if alterations in plasma lipid concentration are present in young adult blacks with only borderline hypertension and if plasma

lipid alterations are linked with insulin resistance.

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Population

This study was conducted in a young clinically well population of blacks, consisting of normotensive and borderline hypertensive men and women. Each participant was drawn from a population that has been under study in ongoing investigations of BP regulation since adolescence.[13 16 17] At enrollment for this study, the age range of the subjects was 28 to 33 years. As in previous studies, we categorically defined the participants as normotensive (BP <135 mm Hg systolic and <85 mm Hg diastolic) or borderline hypertensive (BP ≥135 and <150 mm Hg systolic or ≥85 and <96 mm Hg diastolic), on the basis of repeated measurements of BP.[12 18] Individuals with either IDDM or NIDDM were excluded. No subject was taking antihypertensive medication at the time of study. We used an OGTT to measure plasma glucose and insulin concentration after a standard glucose challenge. A euglycemic hyperinsulinemic clamp procedure was used to quantify insulin-stimulated glucose utilization. Plasma lipids were assayed from blood samples obtained after an overnight fast. The protocol for this study was approved by the Institutional Review Board of the Medical College of Pennsylvania. Written informed consent was obtained from all participants at the time of enrollment.

Enrollment assessment consisted of physical examination, anthropometric measurements (height, weight, skinfold thickness, and circumference of arm, hips, thigh, and waist), and BP determination. Casual systolic (first phase) and diastolic (fifth phase) BP measurements were obtained by auscultation with a mercury column sphygmomanometer with subjects in the seated position after a 10-minute rest period. The average of two determinations was used as the BP at the time of the metabolic evaluation. From the anthropometric measurements, percent body fat[19] and fat free mass[20] were calculated. A history of the subject's diet was taken and each was asked to continue usual dietary patterns through completion of the protocol. For this population, the dietary average consisted of protein 14%, fat 31%, and carbohydrate 55%. No subject had a diet that deviated significantly from this average. After the enrollment assessment, each subject returned to the clinical research unit for an OGTT that was scheduled in the morning after a 12-hour fast. After a fasting blood sample was obtained, a 75-g glucose solution (Glucola, Ames Laboratories) was taken orally. Blood samples were obtained at 30, 60, and 120 minutes after ingestion of the glucose load. Each blood sample was immediately centrifuged. Plasma was removed and stored at -80°C until the samples were assayed for glucose and insulin concentration. Fasting blood was also obtained for measurement of serum lipids. The sample was sent to the Lipid Research Laboratory of the Hospital of the Medical College of Pennsylvania, where total cholesterol, HDL-C, and total TG levels were analyzed by standard enzymatic methods and an automated analyzer (Hitachi 704). HDL-C was isolated according to the method of Bachorik et al.[21] LDL-C was calculated by the Friedewald[22] equation. ApoA-I, apoB, and Lp

(a) were assayed turbidimetrically by using commercial antibodies (Boehringer Mannheim).

The euglycemic hyperinsulinemic clamp was used to measure insulin-stimulated glucose utilization.[23] [24] During steady state hyperinsulinemia, the glucose infusion rate required to maintain euglycemia quantifies insulin-stimulated glucose metabolism (M in $mg \cdot kg^{-1} \cdot min^{-1}$). In both nonobese and obese young black men, we have demonstrated that with steady state hyperinsulinemia at a level of 70 to 80 μU/mL greater than fasting insulin level, endogenous glucose production is completely suppressed during the final 60 minutes of the procedure.[25] Because the target level of steady state hyperinsulinemia in the present study was at least 70 to 80 μU/mL greater than fasting insulin level, endogenous glucose production is completely suppressed, and the glucose infusion rate required to maintain euglycemia (M) is an adequate index of total insulin-stimulated glucose utilization.[24]

Each subject returned to the clinical research unit for the euglycemic clamp procedure at 8 AM after a 12-hour overnight fast. The euglycemic clamp procedure was conducted according to methods previously described.[12] In brief, the subject rested for at least 20 minutes after placement of venous catheters for infusion and sample withdrawal. Before the onset of euglycemic hyperinsulinemia, three samples were withdrawn for determination of fasting plasma glucose and fasting plasma insulin concentration. Euglycemic hyperinsulinemia was established with a primed constant infusion of insulin using the method of Rizza et al[24] to compute the priming dose and infusion rate of insulin. The target clamped-insulin concentration was 70 to 80 μU/mL of insulin above fasting concentration, which was achieved with an infusion rate of 40 $mU \cdot m^{-2} \cdot min^{-1}$.[24] Glucose infusion was administered as 20% dextrose. The precise glucose concentration in the 20% dextrose stock solution was measured, and this value was used in the calculation of the glucose infusion rate with the negative feedback equation of DeFronzo et al.[23] A personal computer was programmed to use this iterative negative feedback equation, which was amended for 10-minute plasma glucose sampling. Euglycemic hyperinsulinemia was maintained for 120 minutes. During the final 60 minutes of steady state hyperinsulinemia, insulin-stimulated glucose utilization was determined from the glucose infusion rate. The coefficient of variation for clamped plasma glucose concentration was less than 5% during the final 60 minutes of the procedure. Insulin-stimulated glucose utilization was computed as the mean glucose infusion rate during the final 60 minutes of hyperinsulinemia and expressed as $mg \cdot kg^{-1} \cdot min^{-1}$ (M). Using the anthropometric measures, we computed fat free mass for each subject, and insulin-stimulated glucose utilization was also expressed as $mg \cdot kg^{-1}$ fat-free mass $\cdot min^{-1}$ (M').

Glucose was administered as 20% dextrose in water (Abbott). Insulin (Eli Lilly) was mixed with normal saline to a concentration of 1000 mU/mL. All solutions were delivered by syringe pumps (Harvard model 22). Plasma glucose concentration was analyzed with the glucose oxidase technique (YSI model 27, Glucostat). Plasma insulin concentration was determined with a solid-phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corp). Coefficients of variation for interassay and intraassay variability for glucose, insulin, and the above lipid assays are less than

5%.

Data Analysis

Two-way ANOVA was used to test for significant differences in means (normotensive subjects versus hypertensive subjects, and men versus women). Tests for interactions were conducted between BP groups and gender groups. Instead of using a repeated-measures ANOVA and post hoc *t* tests for the OGTT data, we used the sum of the insulin levels during the OGTT as the parameter in the categorical or continuous data analysis. Differences in means and interactions were considered statistically significant at $P<.05$. Univariate correlations among numerically continuous variables were examined by using Pearson correlation coefficients. Stepwise multiple linear regressions were used to examine multiple correlations among variables and to build a regression model for insulin-stimulated glucose utilization (M) by the other variables. On the basis of a theoretical model that variables in several categories will significantly determine both M and M', a stepwise multiple linear regression analysis was used to determine the model of best fit of M and M' by independent variables in several categories. All variables in all categories were entered simultaneously in the stepwise regression analysis. The anthropometric variables were BMI, height, weight, and percent body fat. The hemodynamic variables examined were systolic BP, diastolic BP, and mean BP. Metabolic variables were fasting plasma insulin concentration, fasting plasma glucose concentration, the ratio of fasting plasma insulin to glucose concentration, and the sum of plasma insulin concentration during the OGTT. The plasma lipid parameters examined included total cholesterol, HDL-C, LDL-C, TGs, apoA-I, apoB, and Lp(a). The stepwise computer algorithm for the regression equation selects at the first step the highest correlated variable with the dependent variable. At the second step, the algorithm selects the variable that produces the highest canonical correlation based on two independent variables with the dependent variable. Therefore, variables that are highly correlated with the first independent variable entered are usually not entered into the regression. The computer algorithm continues until there are no additional statistically significant ($P<.05$) increases in the prediction of the single dependent variable on the best linear combination of independent variables. There are some highly correlated independent variables such as weight, height, and BMI. The algorithm is not disrupted or negated by this multicolinearity, but once one of a set of highly correlated parameters is entered into the model, and it is usually the strongest correlate with the dependent variable, there is no additional predictive value for others in that set.

Results

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Enrollment assessment and all procedures were completed on 94 subjects including 46 men and 48 women. According to the BP criteria, the sample included 60 normotensive (64%) and 34 borderline hypertensive (38%) subjects. Descriptive data on this clinical sample are provided in Table 1⊞. The participants in this study were within a narrow age range with a mean of 29.9 years. According to definition, those with borderline hypertension had significantly higher

systolic, diastolic, and mean BPs than normotensive subjects. BMI was significantly greater in the borderline hypertensive subjects (P=.004). When fat free mass was computed from the anthropometric measures, the nonadipose body mass was still significantly greater in the borderline hypertensive subjects than in the normotensive subjects (P=.009). The ratio of subscapular to triceps skinfold thickness was used as an index of centrality for body fat distribution.[26] There was no difference between the BP groups in body fat centrality. The higher ratio in the women is consistent with a higher percent body fat compared with men.

View this table: **Table 1.** Characteristics of Black Population Studied
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The parameters of insulin-regulated glucose metabolism and plasma lipids for the BP and gender groups are presented in Table 2. The fasting plasma insulin concentration is greater in the borderline hypertensive subjects of both sexes compared with the normotensive subjects, and this difference is statistically significant by two-way ANOVA (P=.003). Similarly, the ratio of fasting plasma insulin concentration to fasting plasma glucose concentration (I/G) is greater in the borderline hypertensive subjects than in the normotensive subjects; this difference is also statistically significant (P=.003). There are no statistically significant sex differences in these two variables. The sums of plasma insulin concentrations during the OGTT are not significantly different between the BP groups. While the mean value for the sum of plasma insulin concentration is greater in the women, the sex difference does not reach statistical significance (P=.068). Insulin-stimulated glucose utilization (M) determined by the insulin clamp procedure demonstrates a lower M, or relative insulin resistance in the borderline hypertensive subjects compared with the normotensive subjects (P=.006). M is also significantly lower in the women compared with men in each BP group (P=.040). When the rate of insulin-stimulated glucose utilization is corrected for adiposity and expressed as $mg \cdot kg^{-1}$ fat free mass $\cdot min^{-1}$ (M'), the insulin sensitivity remains significantly lower in the borderline hypertensive subjects compared with the normotensive subjects (P=.006), and there are no sex differences in M'. Also shown in Table 2 are the results of the two-way ANOVA of plasma lipid concentrations by BP group and sex. There were no statistically significant differences between normotensive subjects and borderline hypertensive subjects in any of the plasma lipids. There were significant sex differences, with men demonstrating higher TG levels (P=.006) and higher apoB levels (P=.03) compared with women. Women demonstrated higher Lp(a) compared with men (P=.01).

View this table: **Table 2.** Metabolic Parameters for Each Sex—BP Group
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When the relation of BP with insulin sensitivity was examined by correlation analysis on the entire study population, there was a statistically significant correlation of insulin-stimulated glucose utilization, corrected for adiposity, in mg · kg^{-1} fat free mass · min^{-1} (M') with systolic BP (r=-.39, P<.0001), diastolic BP (r=-.22, P=.018), and mean BP (r=-.31, P=.001). The total insulin response to glucose challenge on the OGTT did not show significant differences by BP classification by the two-way ANOVA. However, the univariate analysis on the entire study group demonstrated a statistically significant correlation of the sum of insulin during OGTT with the insulin sensitivity corrected for adipose mass, M' (r=-.56, P<.0001).

The relation of plasma lipids with BP and metabolic parameters was examined by univariate correlation analysis. Table 3 provides a summary of these results. There was a statistically significant correlation of mean arterial BP with TGs (P=.02) and with apoB (P=.019). Total cholesterol correlated significantly with fasting insulin (P=.005) and the ratio of fasting insulin to glucose concentration (P=.004) but did not correlate with sum of insulin or the measures of insulin sensitivity. There was no significant correlation of Lp(a) with the BPs or any of the metabolic parameters. However, HDL-C, LDL-C, TG levels, apoA-I, and apoB demonstrated statistically significant correlations with insulin, both fasting and during the OGTT, and with insulin sensitivity. These correlations remained statistically significant with the insulin sensitivity corrected for adiposity (M'). The lipid fraction that demonstrated the strongest relation with insulin sensitivity was HDL-C (r=.437 for M and r=.382 for M', both P<.0001). The relations of apoA-I with M and M' paralleled those of HDL-C; however, the correlation coefficients were not as high. The Figure depicts the correlation of HDL-C with the corrected insulin-stimulated glucose utilization in mg · kg^{-1} fat free mass · min^{-1}. This significant correlation indicates that the association of lower HDL-C with insulin resistance is independent of body fat.

View this table: **Table 3.** Correlation Coefficients for Metabolic Parameters
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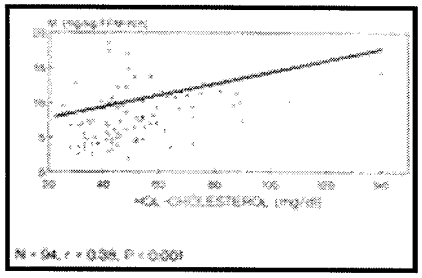

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Figure 1. Insulin-stimulated glucose utilization determined by insulin clamp and expressed in mg/kg fat free mass (M') is correlated with the HDL-C for each subject in the study. HDL-C is presented in the measured values. To convert the measured values of HDL-C to SI units, multiply by .02586.

To examine the relations among the BP, lipid, and metabolic variables, multiple regression analysis was applied to all variables to delineate the major determinants of insulin sensitivity. When M is used as the dependent variable, the statistically significant variables in the regression equation were BMI, systolic BP, sum of insulin, HDL-C, and apoA-I, with a multiple R=.739, P<.0001. To correct for the effect of body fat on insulin resistance, the corrected measure of insulin sensitivity, M', was used as the dependent variable. There was then a statistically significant regression of M' on systolic BP, sum of insulin, HDL-C, and apoA-I. The multiple R for this model is R=.684, P<.0001. The statistics for these multiple regressions are listed in Table 4⊞. The two regression models are markedly similar. M', corrected for body fat, is no longer significantly correlated with BMI, and therefore BMI is not a significant variable in the multiple regression on M'. All other variables remain in the regression model for M'. The magnitude of the slopes, SE of slopes, and the t ratio of slope divided by SE of slope of each of the variables are quite similar between the two regression models. The largest difference between the two models is the value of the constant, which is a function of using M' instead of M as the dependent variable. Overall, highly correlated parameters from each of the four areas (anthropometric, BP, insulin, lipids) contribute to and significantly explain the insulin resistance (M).

View this table: **Table 4.** Multiple Regression Analysis
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The association of hyperinsulinemia, insulin resistance, or both with hypertension in some patients has been established.[8 27] We have previously reported, in a population of young American blacks, lower insulin-stimulated glucose utilization and higher plasma insulin concentration in those with borderline hypertension compared with the normotensive subjects.[12 13] As demonstrated again in this study, young adult American blacks with only borderline hypertension express evidence of insulin resistance with hyperinsulinemia. The insulin resistance, in this population, correlates with plasma lipid concentrations, particularly lower HDL-C concentration. When plasma lipids were compared between normotensive subjects and borderline hypertensive subjects, there were no statistically significant differences in lipids according to BP status. However, the linkage of insulin resistance with BP and with plasma lipid alterations is present and remains significant after adjustment for adipose mass.

Obesity is generally associated with the insulin-resistant syndrome, and hyperinsulinemia is observed under conditions of excessive adiposity. The high percentage of obese subjects in this study, particularly the borderline hypertensive women, would indicate that the insulin resistance may not be entirely independent of obesity. However, we have previously demonstrated relative

insulin resistance in lean borderline hypertensive black men compared with lean normotensive black men,[12] and we have also demonstrated in young blacks that the quantitative measures of insulin resistance are significantly correlated with BP in nonobese subjects having a BMI less than 28.0 kg/m^2.[13] Thus, it is unlikely that obesity per se is a sole causal factor for the linkage of reduced insulin sensitivity and lower HDL-C in those young adults with borderline to mild hypertension.

We have previously reported sex-linked differences in insulin resistance with lower levels of insulin-stimulated glucose utilization, demonstrated in black women compared with black men.[28] Again in this study, both normotensive and borderline hypertensive women had lower insulin sensitivity (M) than the men in the respective BP group. However, when the M value was corrected for adiposity in each subject by expressing insulin-stimulated glucose utilization in mg/kg fat free mass, the sex differences disappeared. Despite somewhat higher plasma insulin concentrations during the OGTT in women, the multiple regression models did not detect sex as a significant variable contributing to insulin resistance in this population.

Elevated plasma insulin concentration, a component of insulin resistance, has been detected in first-degree relatives of patients with NIDDM and is considered to be a significant risk factor for future development of NIDDM.[29 30 31] That elevated plasma insulin also predicts essential hypertension is suggested by recent reports from the San Antonio Heart Study. In a prospective study, elevated fasting insulin levels were found on initial examination in those who were normotensive but who developed hypertension in an 8-year follow-up. In that study, the predictive value of insulin was greater in the nonobese cases.[14] Although Saad et al[11] did not detect a correlation of insulin resistance, measured by insulin clamp, with BP in obese normotensive blacks, the larger CARDIA study on young adults demonstrated a positive association of fasting insulin concentration with BP in both blacks and whites. The strongest correlate of fasting insulin was BMI, but after adjustment for BMI, there was still a significant correlation of BP with insulin in both racial groups.[32]

Insulin resistance is defined as impaired insulin-stimulated glucose utilization.[8] Due to a peripheral cell defect in insulin-mediated glucose metabolism, a greater quantity of insulin is necessary to achieve metabolic control of glucose. Subsequent increases in insulin secretion result in hyperinsulinemia. Ferrannini et al[8 33] have detected a reduction of insulin-stimulated glycogen synthesis in skeletal muscle in nonobese patients with essential hypertension. Subsequent hyperinsulinemia, expressed as a consequence of this defect, may mediate BP elevation through extrametabolic pathways, such as the effect of insulin on sodium transport.[34 35 36] The results of this study are in agreement with this concept. Insulin sensitivity (M and M') as determined by the insulin clamp is significantly lower in the borderline hypertensive subjects compared with the normotensive subjects. Fasting insulin level and the ratio of fasting insulin to glucose are higher in the borderline hypertensive subjects. Although the sum of insulin levels during the OGTT is not significantly different between the two BP groups, a significant relation with BP is present when sum of insulin is examined as a continuous variable in correlation analysis. While insulin

resistance and hyperinsulinemia cosegregate in this study, the weight of the statistical power is consistent with the concept that the hyperinsulinemia is a consequence of the insulin resistance.

Univariate analysis of the plasma lipid data in this study demonstrated significant correlations of HDL-C, LDL-C, TG levels, apoA-I, and apoB with plasma insulin concentration and with insulin sensitivity (M, M'). Total cholesterol, TG levels, and apoB correlated significantly with BP. Lemne et al[37] reported a significant correlation of VLDL, HDL-C, and TG with plasma insulin level in both normotensive and borderline hypertensive men. When the plasma lipid levels were compared between the normotensive and borderline hypertensive groups, VLDL and TG were significantly higher, and HDL-C was significantly lower in the borderline hypertensive subjects than the normotensive subjects. However, most of the group differences in plasma lipoproteins disappeared when corrections were made for BMI or plasma insulin level. Our results are consistent with the CARDIA study on a biracial population of young adult blacks and whites. In a much larger sample of both blacks and whites, fasting plasma insulin level correlated with LDL-C, HDL-C, TG, apoA-I, and apoB after adjustment for covariates of BMI, alcohol intake, and physical activity.[32] Overall, these reports suggest that it is the hyperinsulinemia that mediates the alterations in plasma lipids. In both the CARDIA study and the data reported here, the association of an atherogenic lipid profile with hyperinsulinemia suggests that insulin resistance may be contributing to the risk for cardiovascular disease beyond the risk of hypertension alone in this population.

When all lipid and lipoprotein variables in this study were entered into a stepwise multiple linear regression analysis, HDL-C emerged as the most significant lipid component in the model for insulin resistance. Investigations on racial difference in plasma lipids have reported higher HDL-C in blacks compared with whites.[38] The CARDIA study, which examined young adults 18 to 24 years old, demonstrated higher HDL-C and apoA-I levels in the young black males compared with the white males.[39] Similar racial differences of higher HDL-C levels in young black males compared with young white males were found in the Bogalusa Heart Study.[40] Higher HDL-C was reported in both black males and black females compared with their white age- and sex-matched counterparts in the LRC Program Prevalence Study.[41] Since plasma HDL-C concentration has been shown to be inversely related to coronary heart disease, it has been suggested that the relatively higher HDL-C could account for lower mortality from coronary artery disease in blacks even though blacks have higher rates of hypertension.[38] The association of lower HDL-C with insulin resistance and hyperinsulinemia demonstrated in this study suggests that the cardiovascular protective effect of HDL-C may be lost in young adult blacks with borderline hypertension.

The insulin-resistant syndrome contributes a constellation of risk factors for cardiovascular disease. In this study, impaired insulin-stimulated glucose utilization correlated with BP, plasma insulin concentrations, and atherogenic alterations in plasma lipid levels. Despite the high prevalence of obesity in this black population, these significant relations persisted after adjustment for obesity. The data suggest that in blacks with mild hypertension the risk for

cardiovascular disease may be augmented when the metabolic components of insulin resistance also are present.

Selected Abbreviations and Acronyms

apoA-I	= apolipoprotein A-I
apoB	= apolipoprotein B
BMI	= body mass index
NIDDM	= non–insulin-dependent diabetes mellitus
OGTT	= oral glucose tolerance test
TG	= triglyceride(s)

Acknowledgments

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Footnotes

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Relationship between obesity and the increased risk of major complications in non-insulin-dependent diabetes mellitus

Serrano Rios

Obesity and non-insulin-dependent diabetes mellitus (NIDDM) are closely linked. They frequently occur together in patients, and body mass index (BMI) is the strongest risk factor for the development of NIDDM. Both obesity and NIDDM are also major causes of morbidity and mortality from atherogenic macrovascular disease, and they are independent risk factors for coronary heart disease. The risk of developing NIDDM and cardiovascular disease is affected by the regional distribution of body fat. Visceral obesity is associated with a higher degree of risk than peripheral obesity. The metabolic and circulatory changes associated with visceral obesity lead to the development of insulin resistance and increased lipoprotein synthesis. For example, the change in the population profile of lipoproteins in the blood, and alterations in the levels of oxidative stress lead to an increased cardiovascular and macrovascular risk. The changes in lipid metabolism also affect haemorrheological function. They have been linked to decreased fibrinolysis (a serious cardiovascular risk factor) through elevated levels of plasminogen activator inhibitor factor, high blood viscosity, and increased erythrocyte aggregability. Increased BMI also appears to be associated with endothelial dysfunction, which is a major factor in atheroma plaque formation and development of thrombosis. Visceral obesity therefore adds a significant burden to the already increased cardiovascular risk inherent in NIDDM. However, even moderate weight loss may successfully reverse the majority of changes seen with visceral obesity.

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ApoA-IV polymorphism associated with myocardial infarction in obese NIDDM patients. The San Luis Valley Diabetes Study.

Rewers M, **Kamboh MI**, **Hoag S**, **Shetterly SM**, **Ferrell RE**, **Hamman RF**.

Department of Preventive Medicine, University of Colorado, Denver 80262.

Non-insulin-dependent diabetes mellitus (NIDDM) confers myocardial infarction (MI) risk unexplained by known factors. In 356 NIDDM patients and 1,087 people with normal glucose tolerance, we investigated the association between MI risk and polymorphism at codon 360 in the apolipoprotein A-IV (apoA-IV) gene. During 1984-1992, MI was diagnosed in 84 diabetic and in 106 nondiabetic people. The risk of MI did not differ by apoA-IV phenotype in nondiabetic people; however, in NIDDM patients, those with the apoA-IV 1-2 phenotype had 2.8 (95% confidence interval: 1.4-5.6) higher MI risk than those with the 1-1 phenotype, adjusting for age, gender, ethnicity, hypertension, smoking, body mass index, fat centrality, and low-density lipoprotein and high-density lipoprotein cholesterol. The risk of MI was particularly high in obese NIDDM patients with the apoA-IV 1-2 phenotype: 5.1 (2.4-11.2) times that in obese apoA-IV 1-1 NIDDM patients and 7.7 (3.6-16.7) times that in lean nondiabetic people. The effect of apoA-IV 1-2 did not appear to be a part of the insulin-resistance syndrome nor was it dependent on diabetes duration or control. One half of the excess MI risk in the diabetic population studied was explained by the apoA-IV 1-2 phenotype. These results indicate that approximately 17% of NIDDM patients have a high MI risk apoA-IV phenotype that is particularly deleterious in obese patients.

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Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease.

Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K.

Department of Rehabilitation, Pitea River Valley Hospital, Sweden. niels.andreasen@nll.se

OBJECTIVES: To study the diagnostic potential of the 42 amino acid form of beta-amyloid (beta-amyloid(1-42)) in cerebrospinal fluid (CSF) as a biochemical marker for Alzheimer disease (AD), the intra-individual biological variation of CSF-beta-amyloid(1-42) level in patients with AD, and the possible effects of differential binding between beta-amyloid and apolipoprotein E isoforms on CSF-beta-amyloid (1-42) levels. DESIGN: A 20-month prospective follow-up study. SETTING: Community population-based sample of consecutive patients with AD referred to the Pitea River Valley Hospital, Pitea, Sweden. PATIENTS: Fifty-three patients with AD (mean +/- SD age, 71.4 +/- 7.4 years) diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria and 21 healthy, age-matched (mean +/- SD age, 68.8 +/- 8.0 years) control subjects. MAIN OUTCOME MEASURES: Cerebrospinal fluid beta-amyloid(1-42) level--analyzed using enzyme-linked immunosorbent assay--and severity of dementia--analyzed using the Mini-Mental State Examination. RESULTS: Mean +/- SD levels of CSF-beta-amyloid(1-42) were decreased (P<.001) in patients with AD (709 +/- 304 pg/mL) compared with controls (1678 +/- 436 pg/mL). Most patients with AD (49 [92%] of 53 patients) had reduced levels (<1130 pg/mL). A highly significant correlation (r = 0.90; P<.001) between baseline and 1-year follow-up CSF-beta-amyloid(1-42) levels was found. There were no significant correlations between CSF-beta-amyloid(1-42) level and duration (r = -0.16) or severity (r = -0.02) of dementia. Low levels were also found

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in patients with mild dementia (Mini-Mental State Examination score, >25). CONCLUSIONS: The sensitivity of CSF-beta-amyloid(1-42) level as a diagnostic marker for AD is high. The intra-individual biological variation in CSF-beta-amyloid(1-42) level is low. Low CSF-beta-amyloid(1-42) levels are also found in the earlier stages of dementia in patients with AD. These findings suggest that CSF-beta-amyloid(1-42) analyses may be of value in the clinical diagnosis of AD, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult.

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